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NF2

1996 — 1997

Molecular Biology & Genetics

- Gene for NF2 localized to 22q12 (formal separation of NF1 and NF2) 1987
- • *NF2* gene cloned 1993
  • *NF2* gene product identified as Merlin/ Schwannomin 1993
- Mutation Rate for NF2 is ~6.5 x 10^{-6} 1993
- Two major isoforms (splice variants) of *NF2* identified 1994
- Correlations made between genotype and phenotype:
  •Parry et al.
  •Ruttledge et al.
  •Kluewe et al. 1996
- NF2 gene product shares similarity with the 4.1 family of cytoskeleton-associated proteins – Specifically the ERM proteins 1997

Cellular Biology

- Merlin is expressed in the nervous system, smooth muscle, Schwann cells, melanocytes, RBCs, endothelial cells, and neurons such as Purkinje cells and motor neurons, but not in glial cells 1996
- Immunocytochemistry shows Merlin localized to the cell membrane (filopodia, ruffling membrane, and leading edge) 1996
- Truncated forms of Merlin are not detected in NF2 tumors, suggesting protein instability and degradation 1997
- Merlin self-interaction (N- to C-terminal) is involved in growth suppression 1997
- Merlin co-localized with CD44 and the actin cytoskeleton 1997

Pathobiology

- NF2 mutations detected in ~50%-80% of NF2 tumors 1992+
- Merlin (NF2 mutation) is implicated in breast cancers and colorectal cancers 1994
- Merlin is lost in ~60% of sporadic meningiomas and ~80% of sporadic schwannomas 1994
- Merlin (NF2 mutation) is implicated in mesotheliomas 1995
- Germline mutations in NF2 found in at least two-thirds of all individuals with typical bilateral vestibular schwannoma 1996

Technology/ Animal Models

- Drosophila NF2 mutations isolated and characterized 1997
- Drosophila homologue of NF2 (Merlin) identified 1997
- Inactivation of mouse NF2 gene results in embryonic lethality between day 6.5 and 7.0 1997
- NF2 heterozygous (+/-) mice are developed; predisposed to cancer at advanced age, but don't develop the hallmark tumors of NF2 1997

Imaging, Detection & Diagnosis

- Type 2 neurofibromatosis first described by Dr. Wishart 1820
- Type 1 neurofibromatosis1st identified in the literature by Dr. Friedrich von Recklinghausen 1882
- NF2 characterized by schwannomas of the 8th cranial nerve – can also involve schwannomas of other cranial nerves, meningiomas, ependymomas, and ocular manifestations 1987
- Gadolinium-enhanced MRI made available for imaging, detection and diagnosis of vestibular schwannoma – lesions as small as 2 mm are detectable 1988
- Diagnostic criteria for NF2 outlined:
  •Bilateral masses of the 8th cranial nerve; or
  •1 or more 1st degree relative with NF2 + unilateral vestibular mass of 8th cranial nerve; or
  •2 of the following: neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities 1990
- Two types of NF2 identified:
  (1) Gardner type – mild with late onset and few tumors other than vestibular schwannoma
  (2) Wishart type – severe, early onset with multiple tumors 1992
- Mosaicism at NF2 locus is uncommon and probably under-recognized; unilateral vestibular schwannoma, ipsilateral intracranial tumors, schwannomatosis, and/or asymmetric involvement 1996
- Schwannomatosis described as a separate clinical entity from other forms of NF: multiple schwannomas without evidence of vestibular schwannoma 1996
- Diagnostic criteria for NF2 outlined:
  •Bilateral vestibular schwannoma; or
  •1 or more 1st degree relative with NF2 + unilateral vestibular schwannoma at <30 years; or
  •2 of the following: meningioma, glioma, schwannoma, juvenile posterior lenticular opacities 1997

Epidemiology

- Birth incidence of NF2 is determined to be ~1:33,000-40,000 1992
- Diagnostic prevalence of NF2 is ~1:200,000 because of late onset and early death 1992
- Correlations made between genotype and phenotype:
  •Nonsense/frameshift mutations = severe phenotypes
  •Splice-site mutations = variable phenotype within/ between families
  •Very few non-truncating mutations detected
  •Mutations not detected by exon-scanning = mild phenotype 1996

Experimental Therapeutics

- First auditory brainstem implant for treatment of hearing loss from NF2 1979
- FDA granted an Investigational Clinical Trial of a multichannel Auditory Brainstem Implant for NF2 1994
- Calpain inhibitors or calcium channel-blocking agents could prevent growth/relapse of tumors (in vitro) – more studies required 1995
- Aminoglycosides suppress expression of nonsense mutations of NF2 and modify the neoplastic phenotype of tumor cells in culture 1996
- SU-101 tested in Phase II trial for patients with recurrent malignant gliomas 1997

Symptom Management

- Recommended screening:
  •Routine eye exams
  •Enhanced MRI scanning should occur annually, beginning in the teens
  •Surveillance of at-risk but asymptomatic individuals 1980s
- Total excision of vestibular schwannomas or radiation therapy 1991
- Stereotactic radiosurgery (gamma-knife) available for vestibular schwannoma (typically results in loss of hearing) 1992
- Hearing preservation/ augmentation strategies: hearing aids, cochlear implants, training in lip reading and/or sign language 1992
- Partial excision of vestibular schwannoma in cases of large tumors 1993

Important Meetings & Symposia

- Foundation of NNFF 1978
- NIH Consensus Development Conference on Neurofibromatosis: delineated NF1 from NF2 and diagnostic criteria for each 1987
- Foundation of NF, Inc. 1988
- NIH Consensus Development Conference on Acoustic Neuroma 1991
- DoD Neurofibromatosis Research Program (NFRP) established 1996
- NNFF Clinical Care Advisory Board: Diagnostic Evaluation and Management of NF1 and NF2 1997
- House Ear Institute & NNFF workshop on NF2: reviewed current knowledge, made short-term and long-term goals 1997

Neurofibromatosis Type 2 (NF2)

1998

Merlin lacks the conventional C-terminal actin-binding site, but has other actin-binding sites within its FERM domain
1998

Correlations made between genotype and phenotype:
•Evans et al.
1998

Merlin indirectly associates with the actin cytoskeleton through an interaction with βII-Spectrin
1998

Merlin interacts with hNHE-RF, which localizes to actin-rich structures
1998

Merlin binds Paxillin, which facilitates binding to the cell membrane
1998

Merlin co-localizes with F-actin filaments along the membrane
1998

Merlin constitutively degraded by the calpain system in intact cells; N-terminal 35 kD fragment results
1998

Merlin interacts with β-integrin in differentiating Schwann cells
1998

Naturally occurring mutant NF2 proteins demonstrate altered localizations; C-terminal deletions = cell membrane, N-terminal deletions = perinuclear/cytoplasmic region
1998

NF2 Schwannoma-derived cells have abnormal actin cytoskeletal architecture and proliferation defects
1998

Somatic cell mosaic analysis reveals Drosophila Merlin acts as a tumor suppressor
1998

Families with splice-site or missense mutations or large deletions of the NF2 gene tend to have fewer tumors and later onset
1998

Preliminary work done on growth rate of vestibular schwannomas
1998

MRI annually to screen tumor growth and other intracranial risks + annual audiometric studies to monitor hearing (surgery required when hearing is no longer useful or tumor grows enough to endanger patient)
1998

Middle fossa internal auditory canal bony decompression: useful when a change in hearing is documented (for long-term hearing stabilization)
1998

Translabyrinthine total tumor removal with auditory brainstem implant: used for patients with non-useful hearing or large tumors with brainstem compression
1998

Suboccipital approach total tumor removal: used for smaller, medially based tumors (hearing preservation is unlikely and risk of tumor recurrence is high)
1998

Strategic radiation therapy (gamma knife): used in elderly patients with documented tumor growth – low chance of hearing preservation
1998

1999

Method developed for establishing short-term primary Schwannoma cells in culture
1999

Transgenic mice expressing the 1st 314 amino acids of Merlin are normal
1999

Transgenic mice expressing a mutant NF2 that lacks exon 2-3 develop peripheral nerve sheath tumors and Schwann cell hyperplasia
1999

Phase I trial of SU-101 in children
1999

2000

Merlin interacts with SCHIP-1, a novel protein that interacts specifically with spliced forms of Merlin
2000

HRS interacts with Merlin both in vivo and in vitro
2000

Conditional NF2 knockout mice developed (NF2 disrupted specifically in myelin P0-expressing cells) – develop schwannomas in association with peripheral nerves
2000

Pre-symptomatic diagnosis available for ~66% of all classically affected NF2 patients
2000

FDA approval of Nucleus 24-Multichannel Auditory Brainstem Implant
2000

NINDS Workshop: Defining the Future of Neurofibromatosis Research
2000

2001

High resolution microarray-CGH detected an overall 20.7% detection rate out of 116 NF2 patients with differing severity – found a high frequency of large chromosome 22 deletions
2001

Activation of Rac1 or Cdc42 promotes Merlin phosphorylation (inactivation)
2001

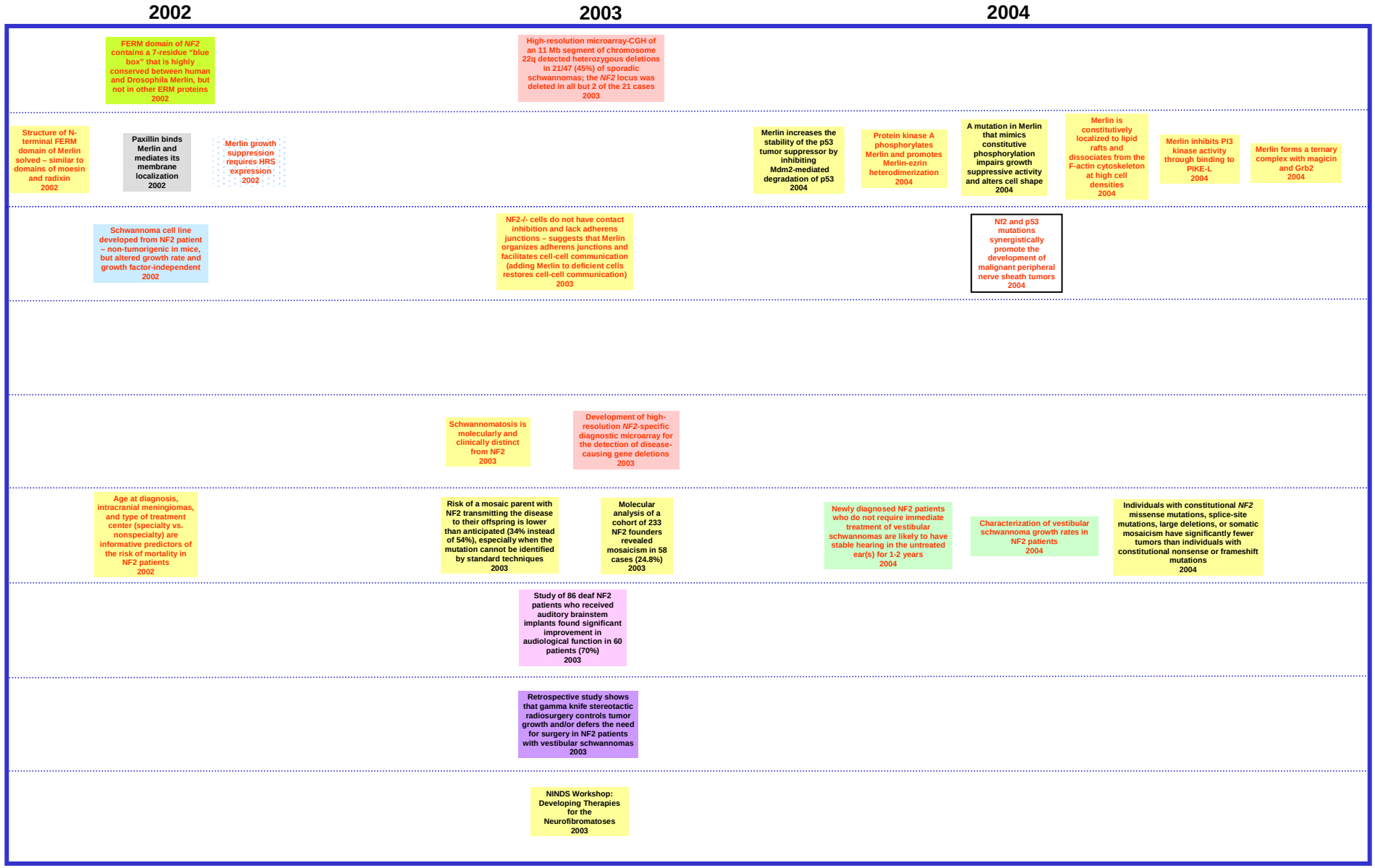
Five multi-allelic complementation groups (including scribbler/brakeless, blistered and net) identified that alter the subcellular localization of Merlin
2001

Syntenin specifically interacts with Merlin isoform 1 – links active Merlin to membrane protein signaling through the actin cytoskeleton
2001

HRS interacts with the C-terminus of Merlin in its open form
2001

Regulated overexpression of HGS in rat schwannoma cells has the same effect as Merlin overexpression
2001

Drosophila Merlin mutants show defects in nuclear migration and mRNA localization in the oocyte
2001


2002
2003
2004
FERM domain of NF2 contains a 7-residue "blue box" that is highly conserved between human and Drosophila Merlin, but not in other ERM proteins 2002
High-resolution microarray-CGH of an 11 Mb segment of chromosome 22q detected heterozygous deletions in 21/47 (45%) of sporadic schwannomas; the NF2 locus was deleted in all but 2 of the 21 cases 2003
Structure of N-terminal FERM domain of Merlin solved – similar to domains of moesin and radixin 2002
Paxillin binds Merlin and mediates its membrane localization 2002
Merlin growth suppression requires HRS expression 2002
Merlin increases the stability of the p53 tumor suppressor by inhibiting Mdm2-mediated degradation of p53 2004
Protein kinase A phosphorylates Merlin and promotes Merlin-ezrin heterodimerization 2004
A mutation in Merlin that mimics constitutive phosphorylation impairs growth suppressive activity and alters cell shape 2004
Merlin is constitutively localized to lipid rafts and dissociates from the F-actin cytoskeleton at high cell densities 2004
Merlin inhibits PI3 kinase activity through binding to PIKE-L 2004
Merlin forms a ternary complex with magicin and Grb2 2004
Schwannoma cell line developed from NF2 patient – non-tumorigenic in mice, but altered growth rate and growth factor-independent 2002
NF2-/- cells do not have contact inhibition and lack adherens junctions – suggests that Merlin organizes adherens junctions and facilitates cell-cell communication (adding Merlin to deficient cells restores cell-cell communication) 2003
Nf2 and p53 mutations synergistically promote the development of malignant peripheral nerve sheath tumors 2004
Schwannomatosis is molecularly and clinically distinct from NF2 2003
Development of high-resolution NF2-specific diagnostic microarray for the detection of disease-causing gene deletions 2003
Age at diagnosis, intracranial meningiomas, and type of treatment center (specialty vs. nonspecialty) are informative predictors of the risk of mortality in NF2 patients 2002
Risk of a mosaic parent with NF2 transmitting the disease to their offspring is lower than anticipated (34% instead of 54%), especially when the mutation cannot be identified by standard techniques 2003
Molecular analysis of a cohort of 233 NF2 founders revealed mosaicism in 58 cases (24.8%) 2003
Newly diagnosed NF2 patients who do not require immediate treatment of vestibular schwannomas are likely to have stable hearing in the untreated ear(s) for 1-2 years 2004
Characterization of vestibular schwannoma growth rates in NF2 patients 2004
Individuals with constitutional NF2 missense mutations, splice-site mutations, large deletions, or somatic mosaicism have significantly fewer tumors than individuals with constitutional nonsense or frameshift mutations 2004
Study of 86 deaf NF2 patients who received auditory brainstem implants found significant improvement in audiological function in 60 patients (70%) 2003
Retrospective study shows that gamma knife stereotactic radiosurgery controls tumor growth and/or defers the need for surgery in NF2 patients with vestibular schwannomas 2003
NINDS Workshop: Developing Therapies for the Neurofibromatoses 2003

NF2

Linked research
Abc NFRP-funded research